UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/666,022 | 09/17/2003 | Dennis M. Klinman | 4239-66899 | 7954 |

7590 09/15/2011

Klarquist Sparkman, LLP
One World Trade Center, Suite 1600
121 S.W. Salmon Street
Portland, OR 97204

| EXAMINER | |
|---|---|
| HORNING, MICHELLE S | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1648 | |

| MAIL DATE | DELIVERY MODE |
|---|---|
| 09/15/2011 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/666,022 | KLINMAN ET AL. | |
| | Examiner | Art Unit | |
| | MICHELLE S. HORNING | 1648 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *11 January 2011*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

5)☒ Claim(s) *1,4-6,9,10,12,13,18-20 and 25* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1, 4-6, 9, 10, 12, 13, 18-20, 25* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

12)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

This action is responsive to communication filed 1/11/2011.

Claims 1, 4-6, 9, 10, 12, 13, 18-20 and 25 are under current examination.

Any objection(s) and/or rejection(s) not reiterated herein have been withdrawn.

### *Continued Examination Under 37 CFR 1.114*

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 1/11/2011 has been entered.

### *Claim Rejections - 35 USC § 103-Necessitated by Claim Amendments*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

**Claims 1, 4-6, 9, 10, 12, 13, 18-20 and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combined teachings of US Patent No. 6977245 (hereinafter as "Klinman"-see attached form 892), Cho *et al.* (*Nature Biotechnology*, 2000-previously cited), Alvar *et al.* (*Clinical Microbiology Reviews*, 1997-previously cited), de la Rosa *et al.* (*J. of Clinical Microbiology*, 2002-previously cited) and US Patent No. 5175267 (hereinafter as "Chu"-see attached form 892).**

The claims are drawn to (in part): a method of increasing an immune response to an opportunistic infection in an immunocompromised subject comprising:

selecting an immunocompromised subject infected with a secondary infection, wherein the immunocompromised subject is immunocompromised as a result of an infection with HIV or SIV, and wherein the secondary infection is infection with *Leishmania*;

administering to the immunocompromised subject infected with the secondary infection a therapeutically effective amount of an oligodeoxynucleotide comprising the nucleic acid sequence set forth as SEQ ID NO: 176, SEQ ID NO: 177 and SEQ ID NO: 178; and

accessing the immune response to the *Leishmania* in the subject;

thereby increasing the response to the *Leishmania* in the immunocompromised subject; see claim 1.

Klinman teaches a method of increasing an immune response to *Leishmania* in a subject comprising administering to the subject a therapeutically effective amount of an oligodeoxynucleotide comprising the nucleic acid sequence set forth as SEQ ID NO: 176, an oligodeoxynucleotide comprising the nucleic acid sequence set forth as SEQ ID NO: 177, and an oligodeoxynucleotide comprising the nucleic acid sequence set forth as SEQ ID NO: 178 and accessing the immune response to the *Leishmania* in the subject. See figure legend of Fig. 7, col. 3, lines 64 to col. 4, disclosing the administration of HKLV (heat-killed leishmainia vaccine) combined with a mixture of D19 (SEQ ID NO: 176), D35 (SEQ ID NO: 177) and D29 (SEQ ID NO: 178) to Macaque monkeys. Following immunization, the author concludes that the Macaques had significantly smaller lesions; see col. 4, lines 5+ and instant claim 1, in part. Note that D19 (SEQ ID NO: 176) comprises the sequence ggtgcatcgatgcagGGGGG; D35 (SEQ ID NO: 177) comprises the sequence GGtgcatcgatgcagggGG and D29 (SEQ ID NO: 178) comprises the sequence GGtgcaccggtgcagGGGGG, wherein the upper caps are phophorothioates and the lower caps are phosphorodiesters; see col. 2, lines 40+ and col. 34, lines 20+. This meets the limitations of claims 9 and 13, and claims 10 and 12, in part. The author describes using a phosphorothioate in the oligonucleotide backbone because such a modification renders the oligonucleotide resistant against degradation and the author teaches the use of a chimeric oligonucleotide comprising both phoshorothioates and phosphodiesters; see col. 10, lines 20+ and col. 13, lines 42.

While Klinman discloses administering a composition comprising the specific sequences set forth by SEQ ID NOs: 176, 177 and 178 to a subject and accessing the

immune response to *Leishmania* (significantly smaller lesions), Klinman does not explicitly express that the *Leishmania* is an opportunistic, secondary infection or the subject is immunocompromised as a result of an infection with HIV or SIV (claims 1 and 25); wherein the HIV is HIV-1 or HIV-2 (claims 4 and 5); wherein the subject has acquired AIDS (claim 6); wherein the nucleotides 2-18 of SEQ ID NO: 177 are phosphodiester bases (claim 10), wherein one or more of nucleotides 1 or 2 of SEQ ID NO: 176 comprise phosphorothioate bases (claim 12); wherein the method of claim 4, further comprises administering to the subject a combination of drugs which comprises HAART (claim 18); the method of claim 1, further comprising administering an anti-retroviral drug, comprising AZT (claims 19 and 20); and, a method of increasing an immune response to an opportunistic infection with a *Leishmania* pathogen in an immunocompromised subject wherein an antigenic epitope of a polypeptide from the pathogen is not administered to the subject (claim 25, in part; see lines 16 and 17).

Cho *et al.* describes the general use of immunostimulatory DNA sequences containing unmethylated CpG motifs for stimulating host defense in subjects with chronic immunosuppression and AIDS (see abstract). Cho *et al.* provide that immunostimulatory DNA sequence-based vaccines have a clinical application in AIDS and other immunodeficiencies and these vaccines may provide protection against opportunistic infection (see p. 513, col. 1 and instant claims 4-6, in part).

Alvar *et al.* describe *Leishmania* as opportunistic pathogens that infect patients with either HIV-1 or HIV-2 (p. 299, col. 2 and p. 312, col. 2 and instant claims 4 and 5).

De la Rosa *et al.* teach that *Leishmania* occurs in HIV-1 infected patients and AIDS-related disorder (see introduction and claims 4 and 6). De la Rosa *et al.* teaches that HAART has a protective effect on the development of *Leishmania* in HIV-infected patients (whole document). The authors disclose that HAART therapy may provide a major impact in countries where HIV-*Leishmania* co-infection is endemic, because *Leishmania* causes morbidity and mortality by itself and enhances the effect of HIV infection in HIV-seropositive patients (see p. 766, col. 2, para. 1 and Table 2, p. 764 disclosing AZT as an anti-retroviral drug of the HAART regimen; see instant claims 18-20).

Chu is cited for showing that AZT is known to inhibit both HIV-1 and HIV-2 replication; see col. 1, lines 19+.

It would have been obvious to one of ordinary skill in the art to use the composition described by Klinman in a method for increasing an immune response to an opportunistic infection in an immunocompromised subject wherein the secondary infection is a *Leishmania* infection. One would have been motivated to do so because Klinman teaches that such composition leads to *significantly* smaller lesions in subjects following administration; see col. 4, lines 5+ of Klinman reference.

Also noted is that the art teaches that sequences comprising unmethylated CpG motif protect against opportunistic infections in AIDS and other immunodeficiencies and a *Leishmania* infection is an opportunistic infection known to occur in HIV-1 and HIV-2-infected patients and AIDS-related disorders. There would have been a reasonable expectation of success given the composition has been characterized to lead to

significantly smaller lesions in a patient infected with *Leishmania* as well as the underlying materials and methods are widely known and commonly used as evidenced by the prior art (*e.g.* making CpG-containing sequences, administration of DNA, *etc.*).

It would have been obvious to one of ordinary skill in the art to incorporate phosphorothioates or phosphodiesters at different positions among the oligonucleotides in the method taught by Klinman. One would have been motivated to do so for the advantage of optimizing results (*e.g.* increasing or decreasing resistance against degradation). There would have been a reasonable expectation of success given the underlying materials and methods are widely known and commonly used as evidenced by the prior art (*e.g.* modification of oligonucleotide backbones, standard molecular biology techniques, *etc.*).

It would have been obvious to further incorporate the use of HAART (which comprises AZT) in the method taught by Klinman. One would have been motivated to do so because the art teaches that HAART has a protective effect on the development of *Leishmania* in HIV-infected patients. Further, the art teaches that AZT is has an inhibitory effect against both HIV-1 and HIV-2 replication. There would have been a reasonable expectation of success given that both HAART and AZT are commonly used and widely known compositions as evidenced by the applied prior art.

Lastly, it would have been obvious to one of ordinary skill in the art to <u>not</u> administer an antigenic epitope of a polypeptide from the pathogen to the immunocompromised subject in the method taught by Klinman wherein the pathogen is *Leishmania*. One would have been motivated to do so for the advantage of establishing

a control response and making comparisons to the results followed by administering the nucleic acid sequences combined with an antigen epitope of a polypeptide from the pathogen in a test subject, such as a Macaque. There would have been a reasonable expectation of success given use of control subjects are widely known and commonly practiced by one of ordinary skill in the art.

The invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

***Response to Relevant Arguments***

It is noted that applicant's arguments with respect to claims 1, 4-6, 9, 10, 12, 13, 18-20 and 25 have been considered but are moot in view of the new ground(s) of rejection. The references by Klinman and Chu are newly cited for the rejection above.

Applicant further argues unexpected results and describes the administration of D ODNs, comprising SEQ ID NOs: 176, 177 and 178, to an SIV-infected and *L. major*-infected subject which lead to the development of significantly smaller lesions. See p. 7-8 of Applicant's Arguments.

The argument has been considered but not found persuasive. As noted above, the prior art reference by Klinman (US Patent No. 6977245) teaches the administration of the claimed combination of ODNs (SEQ ID NOs: 176, 177 and 178) to subjects infected with *Leishmania* and provides that such administration leads to significantly smaller lesions.

The art also teaches that CpG-containing sequences stimulate an immune response in immunocompromised subjects; see Cho *et al. Leishmania* is a known

infection which occurs as a secondary infection in immunocompromised subjects with HIV-1, HIV-2 and AIDS as taught by the Alvar and de la Rosa references. Thus, in view of the prior art teachings, there would have been ample motivation to administer the composition taught by Klinman to immunocompromised subjects in order to increase an immune response against *Leishmania*.

## ***Conclusion***

No claim is allowed at this time.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MICHELLE S. HORNING whose telephone number is (571)272-9036. The examiner can normally be reached on Monday-Friday 8:00-5:00 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, ZACHARIAH LUCAS can be reached on 571-272-0905. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/MICHELLE S HORNING/
Examiner, Art Unit 1648